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ELECTRODES FOR FUNCTIONAL NEUROMUSCULAR STIMULATION

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Section A: Clinical Collaboration

A.1 Primary Collaborator Meeting

In this quarter, a meeting was held with Gordie Polando, a member of the lower extremity research group in Cleveland (VAMC Gait Lab). The lower extremity group primarily uses intramuscular and epimysial electrodes placed in the muscles of the upper leg and are refining their endoscopic technique and specific endoscopic tools to place those electrodes. The group is also working towards the use of nerve cuff electrodes in the upper leg and in the coming months plan to continue development of the necessary endoscopic technique and tools. The iliopsoas, gluteus and hamstrings nerves are sites that have been targeted for nerve cuff implant.

In order to refine their technique, the researchers use fresh frozen cadavers to practice implantation and to identify sites and tissue. A cadaver is scheduled to arrive in the coming weeks and mock endoscopic implants of intramuscular and epimysial electrodes are planned. If time allows following that implant, additional 'practice' will be carried out involving sites and techniques for cuff electrode implant. Members of our lab have been invited to observe and we are particularly interested in familiarizing ourselves with the location and spacing of the implant sites, as well as with the endoscopic technique and tools they have developed.

In the next quarter, we will continue meetings with the upper and lower extremity groups to better understand the clinical issues and directions they are taking. Their specific techniques and procedures will be observed and analyzed for adaptation to spiral cuff electrode implant.

Section B: Electrode Design and Fabrication

B.3 Electrode Materials

Abstract

A series of in vivo tests in rats was begun to test the biological response to alternative silicone rubber and fluoropolymer materials used in the manufacture of electrodes. Silicone rubber nerve cuffs and small segments of fluoropolymer insulated wire were implanted in each of 12 rats. After 2 and 4 weeks, the animals were killed by aortic perfusion and the tissue surrounding the implants was excised for histological processing. A review of the study protocol follows.

Background

As discussed in a previous progress report (QPR #8), several of the original materials used in the construction of our nerve cuff electrodes are no longer available for long-term implant applications. Alternative materials and suppliers have been identified, however the equivalence of these replacement materials for use in cuff electrodes has not been established.

Silicone rubber sheeting serves as the basis for our spiral and helical spiral nerve cuff electrodes and in the past has been made from Dow Corning material, Silastic Q7-4550. An alternative processor has been identified and has manufactured three sheeting batches using three different alternative silicone rubber formulations.

The stainless steel lead wires are insulated in an extruded fluoropolymer and in the past this material has been DuPont's FEP Teflon. A different kind of fluoropolymer formulation, PFA, has been suggested as an alternative and has been used to insulate wire.

The reported physical and mechanical properties of these replacement materials are similar, if not exceeding, those of the originals. Testing results of wire insulated with PFA have been indistinguishable from test results of wire insulated in FEP. No mechanical testing of silicone rubber has been performed to date, although anecdotal observations indicate that the replacement sheetings do have different mechanical and physical properties from each other as well as from the original sheeting. This study was intended to investigate the biological response to both the silicone rubber and fluoropolymer replacement materials.

In Vivo Study

Silicone rubber nerve cuff electrodes were implanted on the sciatic nerves of adult rats. Segments of fluoropolymer insulated wire were placed subcutaneously on the backs of these same animals. Original and replacement materials were used in the manufacture of these implants. Cuffs with and without leads were used to investigate the effects of the lead cable on the resultant tissue encapsulation as well as on the trauma to the nerve. Wire implants of both FEP and PFA were coiled and uncoiled and of two

lengths, short (1 cm) and long (7 cm). Additional "closed helix" lead segments 7 cm long were prepared and consisted of helically wound wires inside of silicone rubber tubing. Two and 4 weeks after implantation, the animals were killed, the tissue was fixed, and the implants with surrounding encapsulation tissue were excised.

Implants

Silicone rubber nerve cuff electrodes without contacts were fabricated according to our standard protocols using 50 µm thick sheeting. The original materials, sheeting made of Dow Corning Silastic Q7-4550 and bonded with MDX4-4210 elastomer, were used in the manufacture of half of the cuffs. The other cuffs were made from alternative materials, sheeting processed by Specialty Silicone Fabricators out of a NuSil formulation and bonded with a NuSil elastomer. The cuffs were manufactured to have a final inner diameter of 1 mm and were cut to a nominal length of 1 cm. All cuffs contained a backbone of three coiled wires and in half of the cuffs this lead extended for a length of several centimeters (>10 cm) beyond the cuff.

After manufacture, the cuffs were cleaned according to the following protocol, with all steps occurring under a laminar flow hood. The cuffs were first sonicated for 20 minutes in a 10% solution of Liquinox in distilled water. The cuffs were rinsed in distilled water until the effluent was free of detergent foam and were then sonicated for 20 minutes each in subsequent solutions of 95% ethanol and ultrapure water. Cuffs were soaked for 48 hours in fresh ultrapure water and then air dried on a clean room wiper.

All cuffs were placed in individual plastic petri dishes and labeled with a 3-digit identification code. The petri dishes were then placed in Chex-All sterilization envelopes which were heat sealed on either end.

Both FEP and PFA insulated wires were used in the manufacture of the subcutaneous implants. In all instances, the wires were comprised of 7-strands of stainless steel coated in approximately 75 µm of fluoropolymer insulation to a final outer diameter of approximately 225 µm. Both straight and coiled and short and long wire implants were prepared. For the straight wires, segments of wire were cut directly from the spool to a length of approximately 5 and 10 cm. A barb was fashioned at one end by bending back a 4 mm length of wire. For the remaining wires, 1 and 10 cm lengths of coil were wound, with uncoiled lengths of wire remaining on either end. A barb was then fashioned at one end using the uncoiled length of wire.

The prepared wire implants were cleaned according to the following protocol, with all steps being carried out under a laminar flow hood. First, the wires were sonicated for a minimum of 5 minutes each in subsequent solutions of Freon TMS and then Safezone. The wires were then rinsed in filtered water and sonicated for a minimum of 5 minutes each in subsequent solutions of 1% Liquinox in filtered water, filtered water, 95% ethanol, and then ultrapure water. The wires were then allowed to dry on a clean room wiper.

The wires were loaded into hypodermic needles before being packaged for sterilization. The needles, 19G for the coiled wires and 22G for the straight wires, were first rigorously cleaned. The cleaning protocol included flushing of the inner bore, immersion and a minimum of 5 minutes of sonication, and then an additional flushing of the inner bore with subsequent solutions of 1% Liquinox in distilled water, filtered water, 95% ethanol, and finally ultrapure water. The needles were left on a clean room wiper under the laminar flow hood to dry.

The wire segments were loaded into the hypodermic needles with the barb being flush at the tip of the needle. The loaded needles were then placed in individual Chex-All envelopes and heat sealed on both ends. The envelopes were labeled with a four-digit code denoting FEP/PFA, uncoiled/coiled, and long/short.

Additionally, a number of implants were prepared which consisted of long segments of coiled, insulated wire placed inside silicone rubber tubing. This type of lead configuration is currently used by our colleagues in the upper extremity. These "closed helix" lead segments were supplied by another laboratory on campus which manufactures these electrodes. A continuous length of uncleaned lead was received and was cut into segments 7 cm in length. Cleaning procedures for these implants were performed at ANCL according to the following protocol. The lead segments were first sonicated for 5 minutes in a 1% Liquinox solution, rinsed in filtered water, sonicated in ultrapure water, sonicated in 95% ethanol, and then allowed to dry on a clean room wiper under a laminar flow hood. The lead segments were then loaded into 15G hypodermic needles that had been cleaned as described above. Metal obtruators to force the implants out of the needle bore were cleaned along with the needles. The loaded needles and obtruators were then placed in individual Chex-All envelopes, heat sealed on both ends, and labeled.

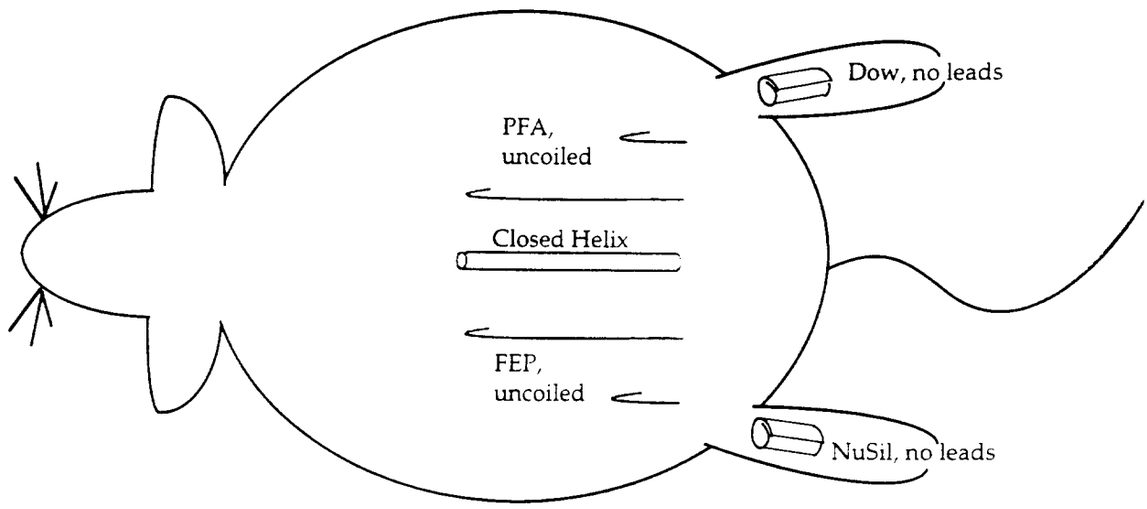
All packaged implants were sterilized by exposure to ethylene oxide and allowed to de-gas for a minimum of 7 days before being used for implant.

Animal Protocol

Twelve adult rats were used in the study with masses ranging from 335-385 g; 6 rats were implanted for 2 weeks, and 6 rats were implanted for 4 weeks. Equivalent implants were placed bilaterally in an animal with 2 nerve cuffs and up to 6 segments of wire being implanted in each animal. This provided for at least 3 samples for each implant type and implant duration. A schematic diagram of the implant and animal groups is provided in the accompanying figures.

Figure 1
4 Week Implant Groups

Rats #1-3
4 week implants



Rats #4-6
4 week implants

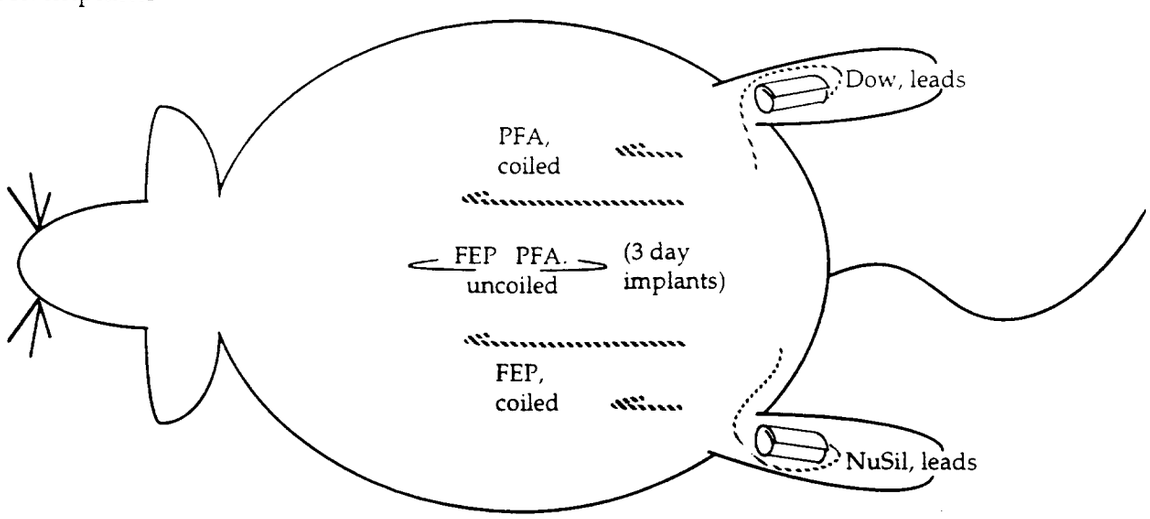
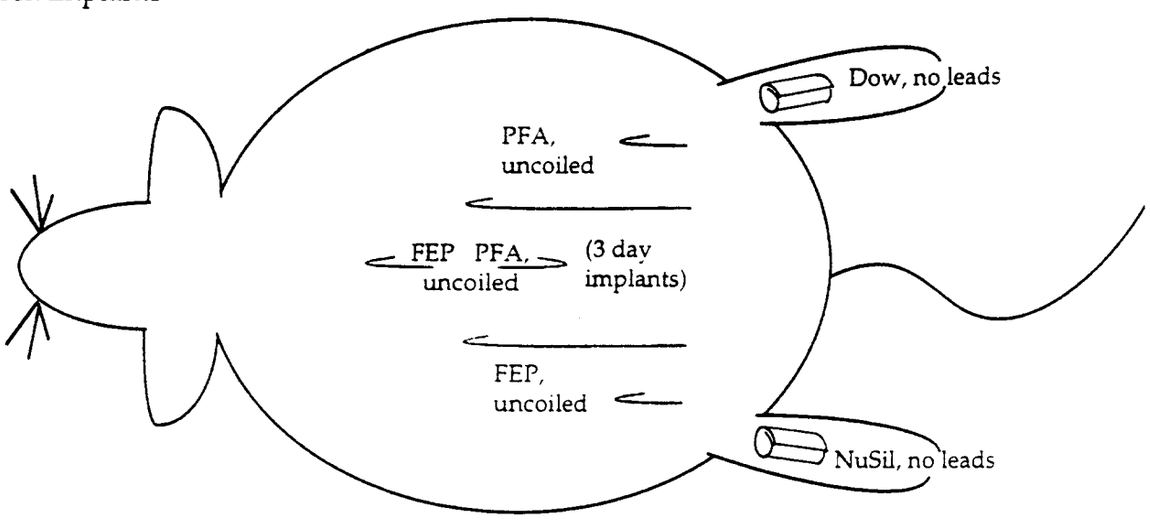
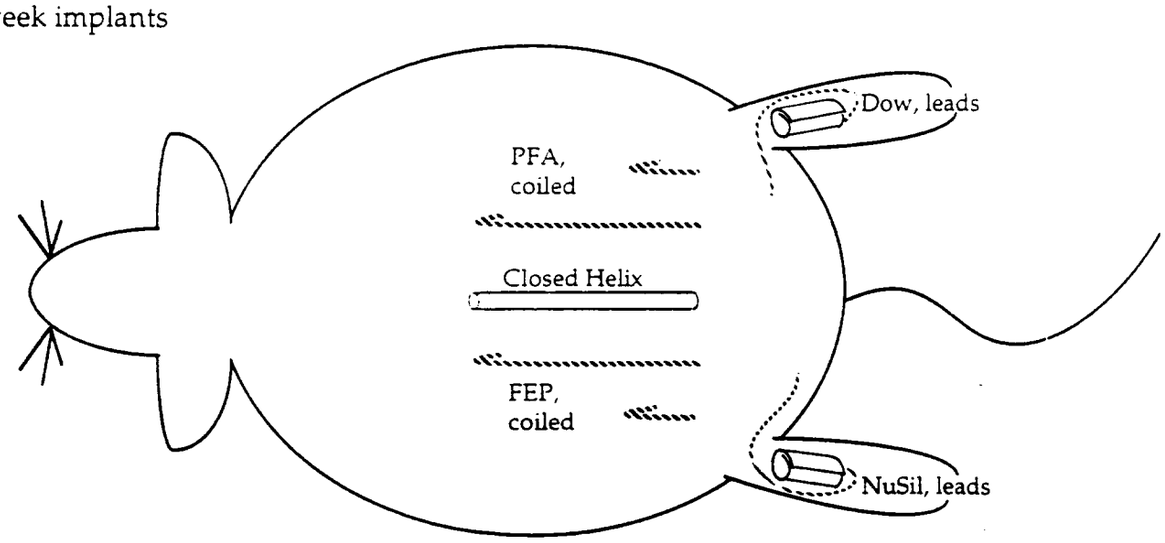


Figure 2
2 Week Implant Groups

Rats #7-9
2 week implants



Rats #10-12
2 week implants



On the day of the implant, the rats were taken to our facility and anesthetized with intraperitoneal (IP) injection of sodium pentobarbital (Nembutal, 40 mg/kg). Once anesthetized, an IP line was established for further drug administration to maintain an acceptable level of anesthesia. The animal was marked for identification using an ear punch. Both hind limbs and the back up to level of the front legs were shaved.

The implant sites were shaved, scrubbed with topical antiseptics (10% povidone-iodine and 95% ethanol) and draped with sterile cloth.

Incisions approximately 2-5 cm were made in each hindlimb overlying the hamstrings muscle. Using blunt dissection, the muscle planes were opened to expose and isolate a 2-3 cm length of the sciatic nerve. Each cuff electrode was soaked in an antibiotic solution of Kefzol and sterile water prior to implant. The electrodes were implanted, one on each sciatic nerve. For those cuffs containing lead wires, the lead cable extended distally from the cuff and a length of lead was looped in the muscle space before being brought to lie subcutaneously at the base of the tail. The muscle fascia was closed using catgut suture, and then the skin incision was closed with Vicryl suture.

After the cuffs were implanted, the wire segments were inserted under the skin of the back. The needles were inserted to lengths of 1 and 7 cm and were then withdrawn. The remaining wire was trimmed close to the skin, and then the skin was pulled taut, bringing the wire fully under the skin. For the "closed helix" segments, an incision approximately 1cm long was made in the midline of the back, several centimeters proximal to the base of the tail. The needle with the closed helix segment was inserted through the incision and run under the skin to a length of 7 cm. The obtruator was used to push the implant out of the needle while the needle was being withdrawn. The incision was then closed using Vicryl suture.

The IP line was removed and the animal was observed until alert and moving. The animals were then returned to their housing facility.

Animals were observed the next day for alertness and mobility. All animals except one were found to be using both hindlimbs for walking and standing upright. In the one animal that did not use both limbs actively, problems were encountered in implanting the cuff on the left limb and excessive time and effort were expended manipulating the nerve. Space limitations and the handling properties of the cuff were the source of the implant problems.

Periodic observations were made of the animals throughout their implant duration. One animal chewed open the sutures on the left hindlimb the day after implant. The animal was re-anesthetized and the site was closed with Vicryl. The next day, the animal had again chewed open the wound. Stainless steel suture was then used to close the site and no further problems were encountered.

For half of the animals, 3 in the 2 week implant group and 3 in the 4 week implant group, additional implants were performed. These implants were short segments of uncoiled wire placed under the skin 3 days before the

animals were scheduled to be killed. These implants were intended to provide acute tissue response data to the FEP and PFA insulation materials.

At the end of the implant period, the animals were killed by aortic perfusion. The animals were fully anesthetized with IP injection of pentobarbital. The animals were placed supine and an incision was made in the skin overlying the peritoneal cavity. The skin was then opened from the peritoneum to the top of the sternum so that remaining work could be performed under direct vision. An incision was made into the peritoneal cavity up to the diaphragm and the base of the sternum. The ribs were cut along the sternum, the chest was opened with rib spreaders and the heart was exposed. A needle was placed into the left ventricle, the tip advanced into the aorta and secured with a hemostat. The needle was attached to a fluid line containing warmed saline solution. The right atrium was cut to allow drainage and the saline was pumped into the circulatory system. Once the fluid flowing out of the right atrium was clear and the liver appeared to clear of blood, the saline flow was stopped and warmed 1% paraformaldehyde in sodium cacodylate buffer was pumped in. This was followed by approximately 600 ml of 3.5% glutaraldehyde solution in sodium cacodylate buffer. When the carcass and tissues felt adequately stiff, the perfusion pump was turned off and the needle was removed from the heart. The hindlimbs were incised to expose the area of the sciatic nerve. The carcass was then soaked in the glutaraldehyde solution and placed in cold storage. Within 48 hours of perfusion, the glutaraldehyde solution was decanted and was replaced with cacodylate buffer solution. The carcasses were then returned to cold storage.

Implant Removal

Several weeks after the perfusion, the carcasses were taken out of cold storage to remove the implants and surrounding tissue encapsulation.

The hindlimbs were further opened using blunt dissection. Skin, muscle and tendon were cut away to expose and isolate the sciatic nerve, the cuff electrode, and the encapsulation tissue. Efforts were made to keep the capsule intact and the cuff on the nerve, although in some instances the fragile nature of the capsule and the manipulations of dissection prevented this. A length of nerve ~1 cm proximal and distal to the cuff was freed and at that point the nerve was cut. The excised section, encompassing the tissue capsule, cuff and nerve, was removed from the limb and placed in a small vial of cacodylate buffer solution. For cuffs with leads, small lengths of lead cable were removed as well.

To remove the wire implants, the skin of the back was slowly peeled away under direct vision. Wire segments were found lying over the muscles of the back or within the tissue directly underlying the skin. A few samples were found to be not subcutaneous, but to have been implanted within the back muscles. The tissue surrounding the wires, including skin and/or muscle tissue, was dissected and removed with the wire. The implants were placed in individual vials of cacodylate buffer solution. For most implants,

identification was made based on relative position. In several cases, however, the wire implants had migrated and their identification was speculative.

Future Work

As the implants and surrounding tissue have been excised, sections will now be prepared for histological processing. Nerve fiber morphology at proximal, distal, and cuff-levels will be investigated. Tissue encapsulation surrounding all wire implants and the cuff electrodes will be studied for extent of inflammatory response.

Section B: Electrode Design and Fabrication
Section C: Assessment of Electrode Performance
Section D: Modifications to Improve Functional Performance

Monopolar vs. Tripolar Configuration:

Background

Ongoing studies of multiple contact spiral cuff electrodes have been described in detail in previous progress reports (QPRs #2-8). In those studies, 12 contact spiral cuff electrodes requiring 12 lead wires were used in acute and chronic tests in cats. The ability of this multiple contact electrode to produce controlled, selective recruitment of the major muscles innervated by the nerve trunk has been demonstrated in those studies.

While the 12 wire lead cable was appropriate for use in animal studies, it presents a significant drawback to the clinical implementation of the cuff electrode. A 12 wire lead cable is deemed not feasible for a long-term human implant. To address this issue, efforts have begun to reduce the number of lead wires required while still maintaining the selective recruitment capabilities of the cuff electrode.

In an earlier study using helical spiral cuff electrodes, the recruitment generated for both monopolar and tripolar stimulation was compared (QPR #4). The results of that study seem to indicate that essentially equivalent recruitment characteristics are achievable with a cuff containing 4 radially placed monopoles as compared to a cuff containing 4 radially placed tripoles. A simplified cuff configuration using monopoles, instead of tripoles has been proposed. A series of experiments were begun to systematically evaluate recruitment characteristics of the two configurations. In those experiments, a single cuff electrode capable of both tripolar and monopolar stimulation was used. This allowed for a direct comparison between the two configurations in the same animal preparation.

Recruitment patterns due to stimulation of nerve cuff electrodes characteristically demonstrate initial muscle recruitment followed by additional muscle(s) activation with increasing current amplitude. This 'spill-over' is to be avoided until full recruitment of the initial muscle has been generated. Work performed by Grill and Mortimer [1993 and in press] using a tripolar cuff configuration has demonstrated the ability to generate full recruitment and avoid spill-over. The work performed here was intended to demonstrate this same capability using a monopolar configuration.

Methods

To compare the tripolar and monopolar configurations, a series of in vivo tests was undertaken. In these tests, a 12 contact spiral cuff electrode is placed on the sciatic nerve of an adult cat in an acute preparation described in

earlier progress reports. The contacts in the cuff are individually addressed through 12 lead wires and can be activated in various combinations to emulate either the tripolar or the monopolar configuration. Tripolar stimulation is achieved by activating the central contact cathodically and the outside two contacts anodically, while monopolar stimulation is achieved by activating the central contact cathodically and using a distant reference (e.g. a percutaneous needle in the nape of the neck) as the return contact. This is illustrated in Figure 3.

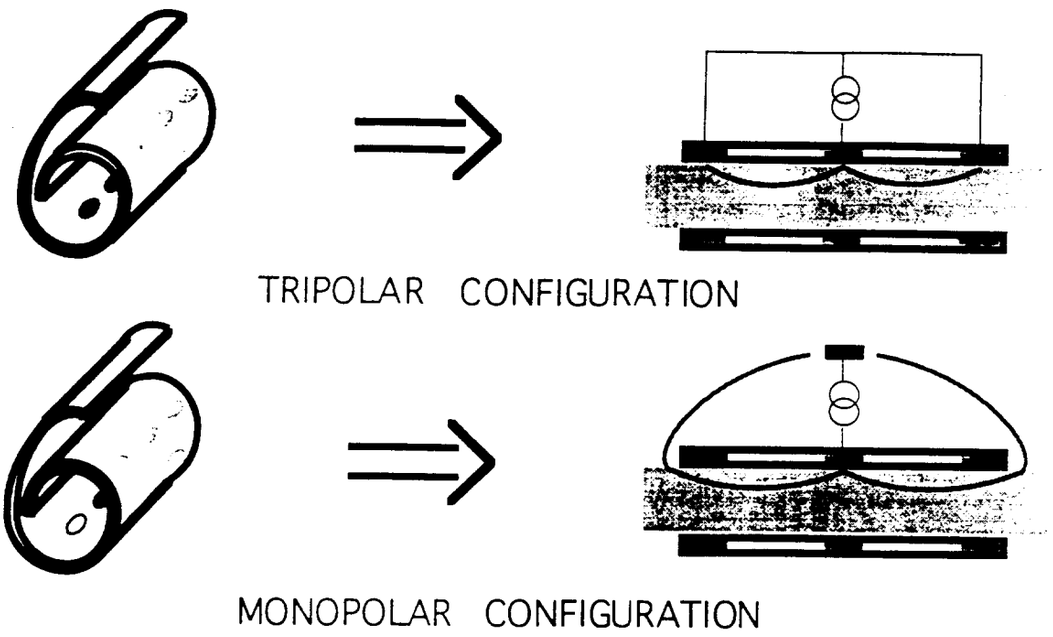


Figure 3: Comparison between the tripolar configuration (top) and the monopolar configuration (bottom) using a 12 contact spiral cuff electrode. Oblique views are given in the left half of the figure, demonstrating the number and placement of electrode contacts in each configuration (open circles represent those contacts not used in monopolar stimulation). Schematics of the longitudinal sections of the cuff in each configuration with symbolic representations of the corresponding electrical circuits are presented on the right side of the figure.

After the electrode is implanted around the sciatic nerve of the cat, the animal's hind limb is placed in a stereotaxic frame, with the paw secured in an instrumented pad designed to measure the torque output at the ankle joint (Grill and Mortimer, in press). Stimulation is applied through the cuff electrode using constant pulsewidth and current amplitude modulation. Joint ankle torque for Plantar/Dorsi Flexion, External/Internal Rotation, and

Eversion/ Inversion is recorded for each tripole and monopole in the cuff at each current amplitude. The data are then presented in moment space, which is the graph of the Plantar/Dorsi Flexion torques versus External/Internal Rotational torques.

In both the monopolar and tripolar configurations the cuff is divided into four quadrants, with the center contact represented as 0°, 90°, 180° and 270°. The 0° position is defined by the set of contacts nearest the end of the cuff. The center contact is stimulated cathodically in all cases. The adjacent contacts are used anodically only in the tripolar configuration.

Previous studies have demonstrated that there is both a change in threshold and gain between monopolar and tripolar stimulation. Due to these differences in threshold and gain, plots of torque versus current or charge are not directly comparable between monopolar and tripolar stimulation. However, comparable torque vectors and magnitudes are expected between monopolar and tripolar stimulation when current or charge amplitude is ignored.

Results

To date, studies have been performed on 3 animals. Data from 1 animal are presented in Figure 4. Data for the other 2 animals in the study are not presented here. The results obtained in those animals follow the trends shown in Figure 4, although less complete sets of data were recorded.

In the figure presented here, the recruitment data generated in each quadrant for both monopolar and tripolar stimulation are presented in one of four panels. In all panels, the tripolar data are plotted using open squares and dashed lines, while the monopolar data are plotted using filled circles and solid lines.

In general, the recruitment trends for both stimulation configurations closely follow one another. The traces for monopolar and tripolar stimulation are very similar in all cases at low stimulus amplitudes and in two cases even at increased stimulus amplitudes. However, at the 90° and 270° positions (panels B and D), the monopolar stimulation resulted in a greater recruitment range than did the tripolar stimulation. In panel B, tripolar stimulation generated a maximum of -15 N-cm external torque and a maximum of 100 N-cm plantarflexion torque, while the monopolar stimulation reached maximums of -30 N-cm and 300 N-cm respectively.

After the data were processed, it was realized that the maximum current allowed for monopolar and tripolar activation were limited to the same pre-set level. Since tripolar electrodes confine the excited area much better than monopolar electrodes, the current limits were reached at two different levels of recruitment. It is likely that in these two cases, had the current amplitude during tripolar stimulation been increased above the pre-set level, the recruitment would have continued to follow that generated by the monopolar stimulation, as occurred at low stimulus amplitudes.

Future Work

Additional studies are planned in the coming quarter(s). In those studies, complete sets of data will be recorded and current amplitudes will be set at levels appropriate for both monopolar and tripolar stimulation.

References:

Grill, WM and JT Mortimer (1993) "Functional control of joint torque with a cuff electrode." Proceedings 15th Annual Intl. Conf. IEEE-EMBS, San Diego, CA.

Grill, WM and JT Mortimer (in press) "Non-invasive measurement of the input-output properties of peripheral nerve-stimulating electrodes." J Neurosci Methods.

Grill, WM and JT Mortimer (in press) "Quantification of recruitment properties of multiple contact cuff electrodes." IEEE Trans Rehab Eng.

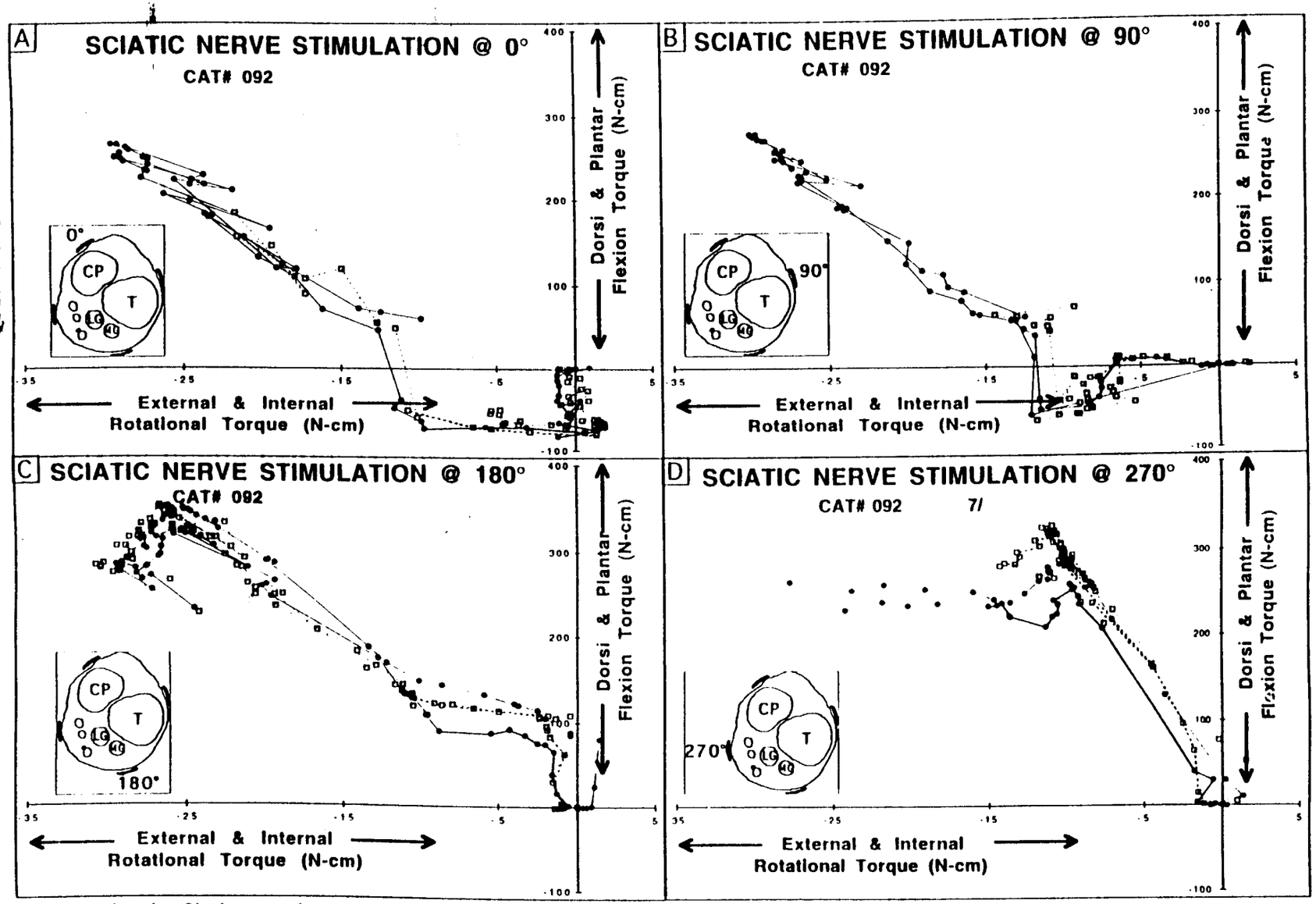


Figure 4: Results of both monopolar and tripolar stimulation as depicted in moment space. Monopolar data are presented with filled circles and solid lines, while tripolar data are presented with open squares and dashed lines. The data are presented in 4 panels for each of the positions around the cuff, as is shown in the panel inserts. In those inserts, a cross-sectional schematic of the nerve is depicted, with the major branches of the sciatic nerve identified.

Section C: Assessment of Electrode Performance

C.3 Removal and Replacement of Encapsulated Spiral Cuff Electrodes

Background

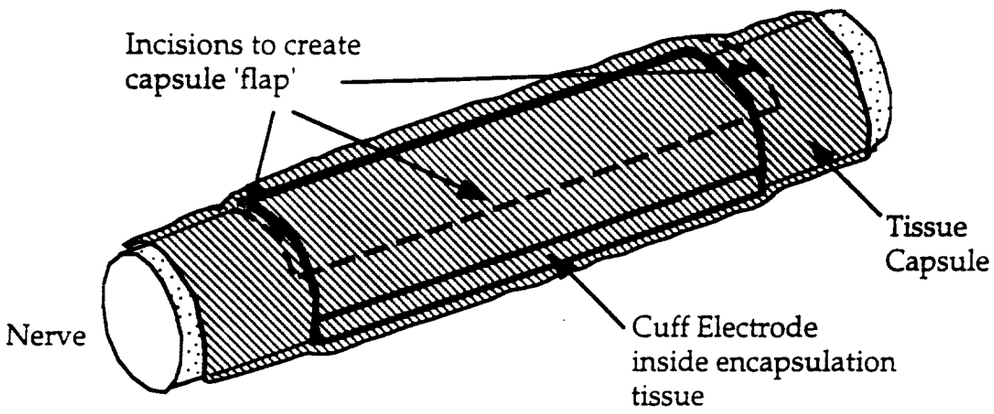
These studies were performed to establish the feasibility of removing and replacing a cuff electrode once it has been encapsulated by connective tissue. These procedures would be necessary in the event that an implanted cuff would require replacement due to defect, damage, or other cause. A preliminary trial has been performed.

Methods

Chronic spiral cuff electrode implants were performed bilaterally on 1 adult cat using aseptic technique and following our standard implant method. On a fully anesthetized animal, the hind portion of the upper leg was surgically opened just proximal to the popliteal fossa and the muscle planes were separated to expose the sciatic nerve. Care was taken to free the nerve trunk from the surrounding tissue with minimal disturbance to the nerve. Once the nerve was isolated, the cuff was carefully placed around the nerve and the site was sutured closed.

The animal was maintained for 4 weeks to allow the connective tissue to encapsulate the cuff. Following this incubation period, a second surgical procedure was performed to remove and replace the electrode. On a fully anesthetized animal, each surgical site was re-opened, and the sciatic nerve was exposed to locate the encapsulated cuff. To remove the original implant, the tissue capsule was carefully incised along both sides and the length of the cuff using fine forceps and spring scissors. This created a flap of encapsulation tissue which was folded back to expose the spiral cuff inside, as is shown in Figure 5. The end of the cuff was located by probing the edge of the cuff and lifting out a single layer of material, as is demonstrated in Figure 6. It was found that the cuff easily slid out of the capsule using this technique. This process could be repeated as necessary to remove additional wraps of the cuff or the end of the cuff could simply be firmly grasped and pulled, sliding the cuff around the nerve and out of the capsule. After removal of the original implant, a replacement cuff was placed in the same surgical site. The inner wrap of the replacement cuff was inserted into the capsule through the excised opening, fed around the back of the nerve, and then wrapped around the nerve, placing the cuff inside of the existing encapsulation tissue. The procedure could not be repeated on the contralateral limb because the cuff had displaced from the nerve. The removal and replacement process was performed under a surgical microscope and video taped for future reference. The animal was killed by bolus injection of pentobarbital and the nerves and remaining encapsulation tissue were then excised and placed in fixative.

Cuff Enclosed in Encapsulation Tissue



Cuff Exposed Through Encapsulation Tissue

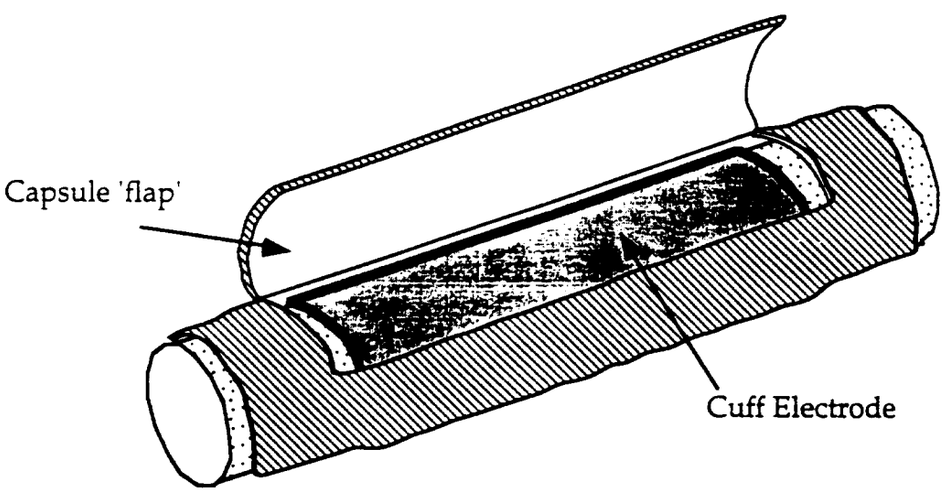


Figure 5: Schematic demonstrating how the encapsulation tissue was opened to expose the cuff.

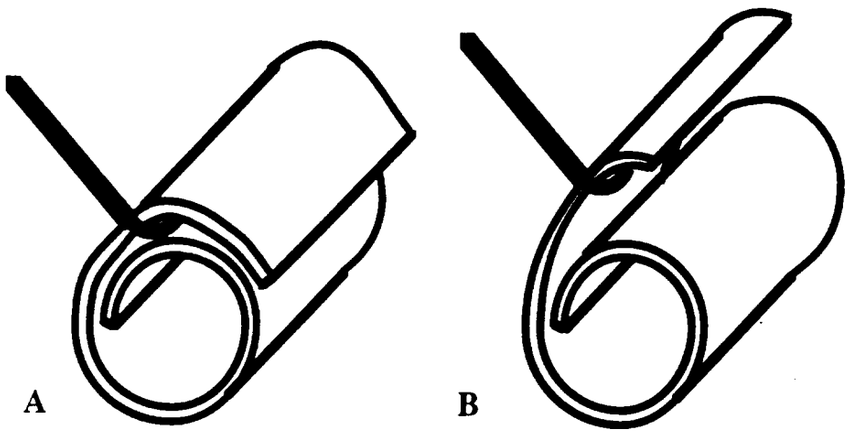


Figure 6: Schematic demonstrating the use of a probe to lift the corner and expose the edge of the implanted cuff.

Conclusions and Future Work

In this trial, the removal and replacement of the cuff was an easy, straight-forward procedure. It is anticipated that an experienced surgeon would have little difficulty in removing and replacing an encapsulated cuff electrode. Specialized tools have been proposed that may simplify the procedure.